

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PO31378WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03168	International filing date (day/month/year) 24.07.2003	Priority date (day/month/year) 02.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D409/04		
Applicant ARGENTA DISCOVERY LIMITED et al.		

<p>1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 29.12.2003	Date of completion of this report 12.11.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fritz, M Telephone No. +49 89 2399-2792



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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-206 as originally filed

Claims, Numbers

1-34 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 28-34

because:

 - the said international application, or the said claims Nos. 28-34 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - the written form has not been furnished or does not comply with the Standard.
 - the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-27
	No: Claims	
Inventive step (IS)	Yes: Claims	1-27
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 28-34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: JUNG M ET AL: 'Analogues of trichostatin A and trapoxin B as histone deacetylase inhibitors' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 13, 8 July 1997 (1997-07-08), pages 1655-1658, XP004136274 ISSN: 0960-894X
- D2: WO 02 26696 A (ROMERO MARTIN MARIA ROSARIO ;FINN PAUL W (GB); HARRIS C JOHN (GB);) 4 April 2002 (2002-04-04)
- D3: RICHON V M ET AL: 'A CLASS OF HYBRID POLAR INDUCERS OF TRANSFORMED CELL DIFFERENTIATION INHIBITS HISTONE DEACETYLASES' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, no. 6, 17 March 1998 (1998-03-17), pages 3003-3007, XP001120542 ISSN: 0027-8424
- D4: WO 00 66555 A (ZHANG PUWEN ;ZHI LIN (US); FENSOME ANDREW (US); JONES TODD K (US);) 9 November 2000 (2000-11-09)

The present application describes compounds of the general formula (I) (claims 1-25), the compounds (I) for use in therapy (claim 26), the usage thereof for the preparation of a medicament (claim 27) and methods of treatment by administering the compounds (I) (claims 28-34).

For the assessment of the present claims 28-34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a

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compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The compounds disclosed in the present case are useful as inhibitors of histone deacetylase.

Substances displaying histone deacetylase inhibiting activities are known from D1-D3. These known compounds comprise a homo- or heterocyclic moiety and a hydroxamic acid group which are separated from each other by a spacer that is a carbon chain optionally interrupted by heteroatoms.

In contrast thereto in the compounds (I) according to the present case a (substituted) thiophene moiety is directly connected via its 2-position to the hydroxamic acid group thus representing a different class of substances.

The title compound of ex. 60 according to D4 is structurally close to the compounds (I) of the present case, however - due to the special substituents of the heterocyclic ring connected to the thiophene - not a representative thereof.

It is noted that the compounds disclosed in D4 display pharmacological activities, these are - however - completely different from those of the compounds (I) according to the present application.

Therefore the subject-matter of claims 1-27 is novel in the sense of Article 33(2) PCT.

In view of D1-D3 each of which can be considered the closest prior art the problem underlying the present application can be formulated as to provide further compounds which are suitable as histone deacetylase inhibitors.

This problem has been solved, as can be seen in the description.

The compounds (I) are a class of substances which has never been suggested as inhibitors of histone deacetylase, they can - by consequence - not be considered obvious for the man skilled in the art.

An inventive step in the sense of Article 33(3) PCT is therefore acknowledged for the subject-matter of claims 1-27.

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Furthermore the following objections are raised:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

The below listed terms (as employed in the claims according to the present case) are understood by the skilled reader as designating the following chemical groups:

"cycloalkyl"	an unsubstituted, saturated monocyclic hydrocarbon group
"cycloalkenyl"	an unsubstituted, saturated monocyclic hydrocarbon group having one double bond
"aryl"	homoaromatic, unsubstituted mono- or polycyclic group
"heteroaryl"	heteroaromatic, unsubstituted mono- or polycyclic group

In the description (p. 7 ff.) definitions of these terms are found which are different from those above. Hence the claims concerned are not in accordance with the description as requested by Article 6 PCT.

The relative term "lower alkyl" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT). This objection can be overcome by precising the term (cf. p. 19, lines 9-11).